REMARKS

Status of the Claims

Claims 8, 9, 14, 15, 20, 21 and 32 are pending. Claims 8, 9, 14, 15, 20, 21 and 32 stand rejected. Claims 8, 14, 15, 20, 21 and 32 are amended. No new matter is added to the amended claims.

Claim Amendments

Claims 8, 15 and 32 are amended herein to overcome the 35 U.S.C §112 rejections. Amended claim 8 is directed to a method of inhibiting cell-cell interaction comprising contacting the cells with an antibody directed against a peptide consisting of SEQ ID NO: 41 or consisting of SEQ ID No:2 that is derived from a cell surface vascular endothelial growth factor and type I collagen inducible protein consisting of SEQ ID No. 13. This contact of the cell with the antibody blocks the binding of αvβ3 and/or α5β1 integrins to the cell surface vascular endothelial growth factor and type I collagen inducible protein, thereby inhibiting the cell-cell interaction.

Amended claim 15 is directed to a method of treating a patient with a pathological condition caused by integrin-mediated cell-cell interaction. This method comprises administering to the patient an antibody directed against a peptide consisting of SEQ ID No. 41 or consisting of SEQ ID No. 2 that is derived from a cell surface vascular endothelial growth factor and type I collagen inducible protein consisting of SEQ ID No. 13. The antibody, thus administered blocks binding of αvβ3 and/or α5β1 integrins to the cell surface vascular

endothelial growth factor and type I collagen inducible protein, thereby treating the patient with the pathological condition caused by the integrin-mediated cell-cell interaction.

Amended claim 32 is directed to a method of inhibiting angiogenesis and the formation of capillaries in a patient in need of such a treatment. This method comprises administering to the patient a pharmacologically effective amount of an antibody directed against a peptide consisting of SEQ ID No. 41 or consisting of SEQ ID No. 2 that is derived from vascular endothelial growth factor and type I collagen inducible protein (VCIP) consisting of SEQ ID No. 13. The administered antibody inhibits $\alpha v\beta 3$ and/or $\alpha 5\beta 1$ integrin-mediated cell-cell interaction, thereby inhibiting angiogenesis and the formation of capillaries in the patient in need of such a treatment.

Furthermore, claims 14, 20 and 21 are amended to overcome the 35 U.S.C. §112, first paragraph rejection by deleting "a combination thereof" from these claims. Amended claim 14 limits the method of inhibiting cell-cell interaction to inflammation or angiogenesis. Amended claim 20 limits the integrin-mediated cell-cell interaction to inflammation or angiogenesis. Amended claim 21 limits the pathological condition to tumor growth, inflammation or angiogenesis.

Amendment to the Specification

Applicant submits that Table 1 on page 34 was amended in the response mailed August 18, 2005. Applicant encloses a copy of the page 34 with the amended Table 1 along with this response.

Objection under 37 CFR 1.821 (d)

The Examiner has maintained the objection for failing to provide a sequence identifier for each of the individual sequence in table 1, page 34.

As discussed supra, Applicant encloses a copy of amended Table 1 which was included in the response mailed August 18, 2005. Please replace page 34 originally filed on March 29, 2004 with the enclosed page. Accordingly, Applicant respectfully requests the withdrawal of this objection.

Objection for informalities

The Examiner has objected to the following informality in claim 32: the lack of article "an" before "antibody".

As discussed supra, Applicant has amended claim 32 to include "an" before "antibody". Accordingly, based on this amendment, Applicant respectfully requests the withdrawal of this objection.

The 35 U.S.C. §112, First Paragraph Rejection

Claims 8-9, 14-15, 20-21 and 32 are rejected under 35 U.S.C. §112, first paragraph for lack of enablement. Applicant respectfully traverses this rejection.

The Examiner states that specification does not provide enablement for the claims since they are broad in their recitation of sequences of the peptides, the VCIP and the integrins. For instance, the Examiner states that the claims as they are written recite a method comprising administering an antibody against a

peptide with any sequence of SEQ ID NO: 41 or SEQ ID NO: 2 that are derived from any VCIP. According to the Examiner, since there is no structural component feature for VCIP, one skilled in the art will not know what species of VCIP to use. Additionally, the Examiner states that specification identifies only $\alpha v\beta 3$ and $\alpha 5\beta 1$ integrins to bind VCIP. Therefore, one skilled in the art would not know what other integrins interaction with VCIP can be blocked by the claimed antibody. Furthermore, the Examiner states that the specification is not enabled for treating any pathological condition or inhibiting any cell-cell interaction. Hence, the Examiner has maintained this rejection.

Independent claims 8, 15 and 32 are amended as discussed supra. The term "with a sequence" in these claims is replaced by "consisting" as suggested by the Examiner. Based on the amendment herein, Applicant submits that the antibody used in the method claims 8, 15 and 32 is directed against peptides having specific sequences such as SEQ ID No. 41 or SEQ ID No. 2.

Furthermore, the Examiner suggests amending the claim to incorporate the sequence of VCIP as the one with SEQ ID No. 14. Applicant respectfully disagrees with inclusion of this specific sequence in the instant claims. The instant invention demonstrated that incubation of cells (HEK293) expressing wild type VCIP with peptides that comprised RGD motif or with anti-VCIP-RGD antibody generated using the peptide of SEQ ID No. 2 inhibited cell-cell interaction (Example 14; Table 1). The peptide with SEQ ID No. 2 comprises amino acids 173-192 of the VCIP with SEQ ID No. 13. The VCIP with SEQ ID No. 14 just represents the phosphatase domain of human VCIP. This phosphatase domain comprises

amino acids 145-161 of the VCIP with SEQ ID No. 13 and does not include the RGD domain. Hence, the peptide with SEQ ID NO. 2 and SEQ ID No. 41 cannot be derived from VCIP with SEQ ID No. 14. Therefore, Applicant has identifed VCIP in the instant claims as the one with SEQ ID No. 13. Additionally, Applicant has amended the instant claims to include the specific integrins.

Applicant further respectfully disagrees with the Examiner that the specification is not enabled for treating any pathological condition or inhibiting cell-cell interaction for the following reasons. The pathological conditions recited in the instant claims are inflammation, angiogenesis or tumor growth. The instant specification teaches that growth factors and inflammatory cytokines induced expression of VCIP (Example 12). The instant invention investigated the mechanism contributing cell-cell interaction in the above-mentioned cells and demonstrated that the cell-cell interaction was integrin mediated and that VCIP-RGD acted as a cell-associated integrin ligand (Example 15-18). Thus, the integrin mediated cell-cell interaction involving VCIP could also contribute to inflammation. The instant invention also investigated the contribution of VCIP-RGD in adhesion of endothelial cells to extracellular matrix (Example 19).

With regards to angiogenesis, the highly motile behavior of activated endothelial cells is known in the art to be crucial for angiogenesis. Since sprouting of new blood vessels requires cell division in preformed endothelial tissues (for instance, wall of the blood vessel) that is accompanied by migration of the endothelial cells, unnecessary angiogenesis can be prevented by inhibiting the migratory behavior of the endothelial cells (page 40, lines 25-30). The instant

invention examined the role played by VCIP in the endothelial cell migration and angiogenesis by performing *in vitro* assays (Example 21-26) that are considered in the art to correlate with the results that one might expect to see *in vivo*. Mouse model (in vivo) was used to demonstrate that VCIP potentiated tumor growth by promoting tumor angiogenesis and augmented tumor metastasis (Examples 27-29). The instant invention demonstrated that anti-VCIP antibody blocked angiogenesis by inhibiting the formation of new capillaries *in vitro* (Example 29).

Applicant submits that the claim amendments presented herein and the teachings in the instant specification with regard to the utility of the antibody directed against the peptides with SEQ ID No. 2 or 41 in the inhibition of cell-cell interaction and in the various pathological conditions discussed supra satisfy the statue. Thus, the scope of the claimed invention is commensurate with the scope of enablement provided. Accordingly, based on the claim amendments and remarks, Applicant respectfully request the withdrawal of rejection of claims 8-9, 14-15, 20-21 and 32 under 35 U.S.C. §112, first paragraph.

The 35 U.S.C. §102 Rejection

Claims 8-9 and 14 are rejected under 35 U.S.C. §102(b) as being anticipated by **Vassilev** *et al* (Blood 1999 Jun 1; 93(11):3624-3631) as is evidenced by **Bendayan** (J Histochem Cytochem 1995, 43:881-886). Applicant traverses this rejection.

The Examiner points to the following arguments made by the Applicant in the previous response. The Applicant had argued that **Vassilev** *et al.*,

teach that the antibody was directed against a 10 amino acid peptide containing the RGD motif. The Applicant further argued that **Vassilev** *et al* neither taught that the antibody was directed against the 5-amino acid peptide (SEQ ID NO: 41) or the 20 amino acid peptide (SEQ ID NO: 2) nor did it teach that the peptide was derived from VCIP as disclosed by the instant specification. Hence, the Applicant concluded that **Vassilev** *et al* teach each and every element of the claim. For these reasons, the Applicant stated that the ability of the antibody generated using the above-mentioned peptides to block the binding of integrins to cell surface VCIP was not inherent.

The Examiner states that Applicant's argument to limit the referenced antibody to a "10-amino acid peptide containing the RGD motif" in a manner inconsistent with the well-known and art-recognized specificity of antibody interaction with epitopes defined by particular amino acid sequences. In other words, the Examiner states that the art teaches that an antibody "cross reacts" and can bind both proteins although the number of amino acids differ.

Applicant respectfully disagrees with the Examiner conclusion that the reference teachings anticipate the claimed method. **Vassilev** *et al* teach that the antibody was directed against a 10-amino acid peptide containing the RGD motif (page 3624, 2nd col.; last para). Although the peptide of **Vassilev** *et al* and those of the instant invention comprise Arg-Gly-Asp sequence, the rest of the amino acids within these peptides are different. Hence, the peptides differ not only in the number of amino acid residues but also in the type of amino acids. **Vassilev** *et al* do not teach that the antibody was also directed against the 5-amino acid

peptide (SEQ ID No. 41) or 20 amino acid peptide (SEQ ID No. 2) of the instant invention.

Furthermore, it is known in the art of protein chemistry that the manner in which a protein folds varies among different proteins. Therefore, a peptide with 10 amino acids will fold differently compared to the peptide with 20 or 5 amino acids, thereby affecting the orientation of the amino acids within the epitope that is recognized a particular antibody. In other words, the antibody directed against a peptide with 10 amino acids may or may not cross-react with a peptide with 20 or 5 amino acids.

Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient (M.P.E.P. 2112). Since the instantly claimed method uses an antibody directed to the specific peptides, whether an antibody generated against these peptides would block the binding of integrins to cell surface VCIP is not inherent based on the teachings of the references cited by the Examiner. Hence, independent claim 8 and its dependent claims 9 and 14 are not anticipated by **Vassilev** *et al.* Accordingly, based on the claim amendments and above-discussed remarks, Applicant respectfully requests the withdrawal of rejection of claims 8-9 and 14 under 35 U.S.C. 102(b).

The 35 U.S.C. §103 Rejection

Claims 15, 20-21 and 32 are rejected under 35 U.S.C §103(a) as being unpatentable over **U.S. Patent No. 5,807,819** in view of **U.S. Patent No.**

5,567,440 and **Vassilev** *et al* as is evidenced by **Bendayan**. Applicant respectfully traverses this rejection.

The Examiner states that Applicant's arguments filed 1/13/06 attempts to limit the referenced antibody to a 10-amino acid peptide containing the RGD motif in a manner inconsistent with the well-known and art-recognized specificity of antibody interaction with epitopes defined by particular amino acid sequence. The Examiner further states that although the motivation to make the modification is not expressly articulated the **U.S. Patent No. 5,567,440** provides a clear motivation as to why the skilled artisan would substitute the CRGDDVC cyclic peptide taught by **U.S. Patent No. 5,807,819** with anti-RGD antibody taught by **Vassilev** *et al* in a method of inhibiting anglogenesis in a subject. The motivation being that, routes to the interruption of cell-cell interactions typically involve competitive inhibition of these receptor-ligand interactions with either receptor antagonists (e.g. cyclic RGD peptides), antibodies or other competitors. The Examiner states this would enable a person of ordinary skill in the art to recognize the interchangeability of the element shown in the prior art for the corresponding element disclosed in the specification.

To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art to modify the reference or to combine the teachings. Second, there must be reasonable expectation of success. Finally, the prior art reference (or

references when combined) must teach or suggest all claim limitations (M.P.E.P. 2143).

Applicant respectfully disagrees with the Examiner's statement that since it is well-known in the art that antibody interaction with epitopes defined by particular amino acid sequences is specific, the antibody taught by **Vassilev** *et al* that is directed against a 10 amino acid peptide will also recognize the peptides of the instant invention for reasons discussed *supra*. **Vassilev** *et al* does not teach or suggest that the antibody directed against the 10 amino acid peptide would also recognize the RGD motif within the peptides with SEQ ID No. 2 or 41. Thus, Applicant reiterates that the prior art references combined do not teach or suggest all claim limitations.

With regards to motivation, Applicant submits that the combined teachings of the references would motivate one of skill in the art to use a 10 amino acid peptide to generate an antibody that recognized the RGD motif rather than the 20 or 5 amino acid peptides of the instant invention. Assuming *arguendo*, even if one of skill in the art were motivated to generate an antibody as taught by the combined teachings of the prior art references, one would only be trying to arrive at the exact same sequence of the peptides of the instant invention that are capable of inhibiting angiogenesis. It has long been known that trying is not the standard for obviousness. Accordingly based on the claim amendments and above-mentioned remarks, Applicant respectfully requests the withdrawal of rejection of claims 15, 20-21 and 32 under 35 U.S.C §103(a).

The 35 U.S.C. §112, Second Paragraph Rejection

Claims 8-9, 14-15, 20-21 and 32 are rejected under 35 U.S.C. §112, second paragraph for being indefinite. Applicant respectfully traverses this rejection.

The Examiner states that the recitation " a peptide with a sequence of SEQ ID No: 41 or with a sequence of SEQ ID No: 2" recited in claims 8,15 and 32 is ambiguous since it is unclear whether the peptide is attached to, derived from, comprising or consisting of SEQ ID NO: 2 or 41.

Applicant has amended the claims 8, 15 and 32 to replace "with a sequence" with "consisting". Hence, it is clear that the peptide consists of SEQ ID No. 2 or 41. Accordingly, based on these amendments and remarks, Applicant respectfully requests the withdrawal of rejection of claims 8-9, 14-15, 20-21 and 32 under 35 U.S.C. §112, second paragraph.

The 35 U.S.C. §112, First Paragraph Rejection

Claims 14, 20 and 21 are rejected under 35 U.S.C. §112, first paragraph for lack of written description requirement. Applicant respectfully traverses this rejection.

The Examiner states that the instant specification does not support the phrase "inflammation, angiogenesis or a combination thereof" in claims 14 and 20 and "tumor growth, inflammation, angiogenesis or a combination thereof" in claim 21.

Applicant has amended claims 14, 20 and 21 as discussed supra. The amended claims no longer recite "a combination thereof". Accordingly, based on these amendments and remarks, Applicant respectfully requests the withdrawal of rejection of claims 14, 20 and 21 under 35 U.S.C. §112, first paragraph.

This is intended to be a complete response to the Final Office Action mailed May 31, 2006. Applicant submits that the pending claims are in condition for allowance. Applicant also includes an amended Table 1, a Petition for Extension of Time and Form PTO-2038 along with the response. If any issues remain outstanding, please telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted

Date: Sept 15, 2006

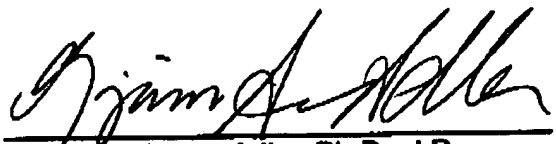

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TABLE 1. Cell Aggregation

HEK cells stably expressing	Substance	Concentration	% cell aggregates
pLNCX2 (vector alone) (V)			0
pLNCX2-VCIP-RGD (WT)			94 ± 5.5[a]
pLNCX2-VCIP-RGE (MT)			0
pLNCX2-VCIP-RGD (WT)	Anti-rabbit IgG	25 μg/ml	90 ± 7.3
pLNCX2-VCIP-RGD (WT)	Anti-rabbit IgG	50 μg/ml	91 ± 8.8
pLNCX2-VCIP-RGD (WT)	Anti-VCIP-RGD	25 μg/ml	73 ± 7.4
pLNCX2-VCIP-RGD (WT)	Anti-VCIP-RGD	50 μg/ml	36 ± 12.5[a]
pLNCX2-VCIP-RGD (WT)	NYRCRGDDSK (SEQ ID NO: 20)	10 nM	67 ± 15.7
pLNCX2-VCIP-RGD (WT)	NYRCRGDDSK (SEQ ID NO: 20)	30 nM	46 ± 13.3
pLNCX2-VCIP-RGD (WT)	NYRCRGDDSK (SEQ ID NO: 20)	50 nM	28 ± 10.5[a]
pLNCX2-VCIP-RGD (WT)	NYRCRADDSK (SEQ ID NO: 21)	10 nM	92 ± 5.7
pLNCX2-VCIP-RGD (WT)	NYRCRADDSK (SEQ ID NO: 21)	30 nM	89 ± 7.5
pLNCX2-VCIP-RGD (WT)	NYRCRADDSK (SEQ ID NO: 21)	50 nM	90 + 7.2[a]

2.0×10^5 HEK cells were pre-treated with indicated substance, washed with PBS, plated in defined media and allowed to form cell aggregates at 37°C. This experiment was carried out using 12-well tissue culture plates. Fresh aliquots of substances were added every 12 h. The number of cell aggregates formed was enumerated at the end of 48 h. Typically, 8-12 cell aggregates were visible in a single 100x microscopic field. At least 5-7 random fields were selected. Experiments were performed three times in triplicate. Values are mean ± SD. [a]$P < 0.05$.